JOC Article

Synthesis of Methyl Carbamates from Primary Aliphatic Amines and Dimethyl Carbonate in Supercritical CO_2: Effects of Pressure and Cosolvents and Chemoselectivity

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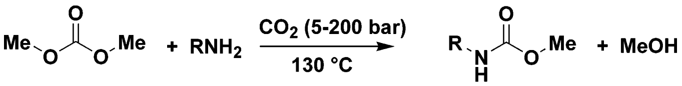

R = $XC_6H_4(CH_2)_n$; n =1: X = H, *o-/p*-OH, *o-/p*-NH_2
n =2: X = H, *p*-NH_2

At 130 °C, in the presence of CO_2 (5−200 bar), primary aliphatic amines react with dimethyl carbonate ($MeOCO_2Me$, DMC) to yield methyl carbamates ($RNHCO_2Me$) and N-methylation side-products (RNHMe and $RNMe_2$). The pressure of CO_2 largely influences both the reaction conversion and the selectivity toward urethanes: in general, conversion goes through a maximum (70−80%) in the midrange (40 bar) and drops at lower and higher pressures, whereas selectivity is continuously improved (from 50% up to 90%) by an increase of the pressure. This is explained by the multiple role of CO_2 in (i) the acid/base equilibrium with aliphatic amines, (ii) the reactivity/solubility of $RNHCO_2^-$ nucleophiles with/in DMC, and (iii) the inhibition of competitive N-methylation reaction of the substrates. Cosolvents also affect the reaction: in particular, a drop in selectivity is observed with polar protic media (i.e., MeOH), plausibly because of solvation effects (through H-bonds) of $RNHCO_2^-$ moieties. The reaction shows also a good chemoselectivity: bifunctional aliphatic amines bearing either aromatic NH_2 or OH substituents [$XC_6H_4(CH_2)_nNH_2$, X = NH_2, OH; $n = 1, 2$], undergo methoxycarbonylation reactions exclusively at aliphatic amino groups and give the corresponding methyl carbamates [$XC_6H_4(CH_2)_nNHCO_2Me$] in 39−65% isolated yields.

Introduction

In the past 2 decades, a number of *phosgene-free* procedures such as the catalytic carbonylation of nitroaromatics,[1] the oxidative carbonylation of amines,[2] and the reaction of amines with carbon dioxide and alkyl halides[3] have been devised for new ecofriendly syntheses of organic carbamates ($RNHCO_2R'$). Among them, the reaction of primary aliphatic amines with dimethyl carbonate (DMC) and gaseous CO_2 is of particular significance from both environmental and synthetic standpoints (Scheme 1).[4] DMC in fact, is a nontoxic reagent available through clean industrial processes: the oxidative carbonylation of MeOH[5] and, more recently, the insertion of CO_2 to epoxides followed by transesterification with MeOH are representative reactions (Scheme 2, paths c and d, respectively).[6]

SCHEME 1. Methyl Carbamates from Primary Aliphatic Amines and DMC/CO_2

$$2RNH_2 + CO_2 \rightleftharpoons RNHCO_2^-\,RNH_3^+ \quad (a)$$

$$RNHCO_2^-\,RNH_3^+ + MeOCO_2Me \longrightarrow RNHCO_2Me + MeOH + CO_2{\cdot}RNH_2 \quad (b)$$

As a part of our long-standing interest on the reactivity of DMC,[5a,7] a few years ago we also undertook an

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[1] Izumi, Y.; Satoh, Y.; Urabe, K. *Chem. Lett.* **1990**, *5*, 795−796.

[2] (a) Cenini, S.; Pizzetti, M.; Crotti, C. In *Aspects of Homogeneous Catalysis*; Ugo, R., Ed.; Riedel: Dordrecht, The Netherlands, 1998, pp 97−108. (b) Aresta, M.; Giannoccaro, P.; Tommasi, I. *J. Organomet. Chem.* **1994**, *476*, 13−18.

[3] (a) Aresta, M.; Quaranta, E. *Tetrahedron* **1992**, *48*, 1515−1530. (b) Yoshida, M.; Hara, N.; Okuyama, S. *Chem. Commun.* **2000**, 151−152. (c) Salvatore, R. N.; Shin, S. II; Nagle, A. S.; Jumg, K. W. *J. Org. Chem.* **2001**, *66*, 1035−1042.

[4] Aresta, M.; Quaranta, E. *Tetrahedron* **1991**, *47*, 9489−9502.

[5] (a) Tundo, P.; Selva, M. *Acc. Chem. Res.* **2002**, *35*, 706−716. (b) Rivetti, F.; Romano, U.; Delledonne, D. In *Green Chemistry: Designing Chemistry for the Environment*; Anastas, P., P. Williamson, P., Eds.; ACS Symposium Series 626, American Chemical Society: Washington, DC, 1996; Chapter 6, pp 70−90.

[6] (a) Bhanage, B. M.; Fuijta, S. I.; Ikushima, Y.; Arai, M. *Appl. Catal. A* **2001**, *219*, 259−266. (b) Bhanage, B. M.; Fuijta, S. I.; He, Y. F.; Ikushima, Y.; Tprii, K.; Arai, M. *Green Chem.* **2003**, *3*, 340−342. (c) Chang, Y.; Jang, T.; Han, B.; Liu, Z.; Wu, W.; Gao, L.; Li, J.; Gao, H.; Zhao, G.; Huang, J. *Appl. Catal. A* **2004**, *263*, 179−186.

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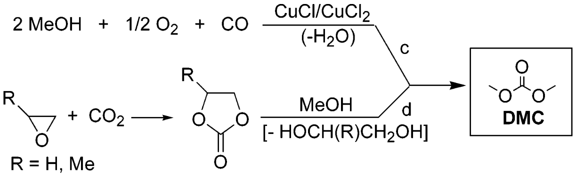
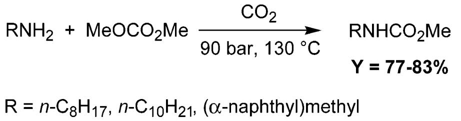
SCHEME 2. Examples of Industrial Synthesis of DMC



investigation of the synthesis of methyl carbamates through the CO_2-promoted reaction of aliphatic amines with dimethyl carbonate;[8] for the first time, supercritical ($scCO_2$) rather than gaseous carbon dioxide was used (Scheme 3). We noticed a beneficial effect on the reaction when the CO_2 pressure was increased from 8 to 90 bar. For instance, in the case of *n*-decylamine, selectivity and yield toward the desired product (n-$C_{10}H_{23}NHCO_2Me$) were improved from 76% to 96% and from 51% to 77%, respectively.

SCHEME 3

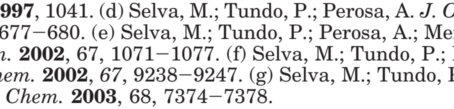


We wish to report herein a further examination of some aspects the carbamate synthesis carried out with DMC and $scCO_2$. In particular, this study shows that (i) the role of the CO_2 pressure (in the range of 5−200 bar) over the selectivity/conversion of the reaction is plausibly related to opposite effects on the two steps (a and b) of Scheme 1; (ii) the presence of cosolvents (MeOH, DMF, DMSO, and cyclohexane) also alters the selectivity through the solvation of the anionic nucleophiles $RNHCO_2^-$; and (iii) the method is valuable for highly chemoselective reactions: diamines (bearing either aromatic and aliphatic NH_2 functionalities), amino-benzyl alcohols, and hydroxy-benzylamines give only methyl carbamates through the exclusive reaction of aliphatic amino groups.

Results and Discussion

Effect of CO_2 Pressure. Our previous investigation showed that the problem with the selectivity of the synthesis of Scheme 3 was the onset of competitive N-methylation reactions taking place with both the reactant amine and the product urethane (Scheme 4).[8] This was in accordance with the dual (methylating and methoxycarbonylating) reactivity of DMC,[5a,7] but preliminary results also indicated that a higher CO_2 pressure could shift the reaction favorably to the desired compounds ($RNHCO_2Me$).

SCHEME 4. Competitive N-Methylation and N-Methoxycarbonylation Reactions



To investigate this behavior, the synthesis of methyl carbamates with DMC/$scCO_2$ was carried out at different pressures (5, 40, 100, 150, and 200 bar). Three model amines were compared: benzylamine (**2a**), phenethylamine (**2b**, more basic and nucleophilic than **2a**),[9] and the sterically hindered cyclohexylamine (**2c**). Experiments were run at 130 °C, in a stainless steel autoclave (equipped with sapphire windows) loaded with a 1.04 M solution (10 mL) of the amine **2** in DMC (molar ratio DMC/**2** = 10) and with CO_2 to the indicated pressure. All reactions were stopped after 2 h. Both the amine conversion and the product distribution were determined by GC, and the structures of all products were assigned by GC−MS and ^1H NMR and by comparison to authentic samples. Each reaction was repeated three times to check for reproducibility. Table 1 reports the results.

In the case of benzylamine (entries 1−7), besides its N-methylated derivatives (**3a**, BnNHMe and **4a**. $BnNMe_2$) and methyl carbamates (**5a**, $BnNHCO_2Me$ and **6a**, $BnN(Me)CO_2Me$), a further product, *N*-benzylidenebenzylamine (**7a**, $PhCH_2N{=}CHPh$), not shown in the table, was detected. The amount of **7a** increased from 3% to 11% as the CO_2 pressure was raised from 3 to 198 bar.[10] In the cases of phenethyl- and cyclohexyl-amines (**2b,c**), no other products were observed but those reported in Table 1.

Two relevant aspects emerge clearly from the reaction of all the three amines:

(i) As the pressure of CO_2 is increased, the reaction conversion increases as well to reach a maximum in the proximity of 40 bar (entries 4, 9, and 14). Conversion drops as the operating pressure is raised beyond this point. The trend is the same for all three amines; the effect is more pronounced for cyclohexylamine. A direct comparison is conveniently depicted in Figure 1.

A general premise should be made before discussing these results. At ambient temperature, as soon as solutions of amines **2a**−**c** in DMC come into contact with CO_2, a rapid precipitation of $RNH_3^+RNHCO_2^-$ as a white solid occurs.[11] Under the conditions of Table 1 (at 130 °C), alkylcarbamate salts melt and the reaction proceeds in two phases (molten salt/liquid solution). However, thanks to the comparable lipophilicity of benzyl, phenethyl, and cyclohexyl substituents, it is realistic that both amines **2a**−**c** and the corresponding carbamate salts have a similar solubility in the liquid DMC/CO_2 phase. The relative comparison of reaction outcomes in Table 1 and Figure 1 appears therefore reliable.

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[7] (a) Selva, M.; Marques, C. A.; Tundo, P. *J. Chem. Soc., Perkin. Trans. 1* **1994**, 1323−1328. (b) Tundo, P.; Selva, M. *Chemtech* **1995**, *25*, 31−35. (c) Selva, M.; Bomben, A.; Tundo, P. *J. Chem. Soc., Perkin. Trans. 1* **1997**, 1041. (d) Selva, M.; Tundo, P.; Perosa, A. *J. Org. Chem.* **2001**, *66*, 677−680. (e) Selva, M.; Tundo, P.; Perosa, A.; Memoli, S. *J. Org. Chem.* **2002**, 67, 1071−1077. (f) Selva, M.; Tundo, P.; Perosa, A. *J. Org. Chem.* **2002**, *67*, 9238−9247. (g) Selva, M.; Tundo, P.; Perosa, A. *J. Org. Chem.* **2003**, 68, 7374−7378.

[8] Selva, M.; Tundo, P.; Perosa, A. *Tetrahedron Lett.* **2002** (43), 1217−1219.

[9] (a) Swain, C. G.; Scott, C. B. *J. Am. Chem. Soc.* **1953**, *75*, 141−147. (b) Pearson, G. R.; Sobel, H. Songstad, J. *J. Am. Chem. Soc.* **1968**, *90*, 319−326. (c) Bock, L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 2826−2829.

[10] In Table 1 (entries 1−7), the difference between the reaction conversion and the total amount of products (**3a** + **4a** + **5a** + **6a**) accounts for the quantity of **7a**, whose structure was assigned by GC−MS. The formation of **7a** is in all probability promoted by O_2 traces in the reaction mixture. See: Hirao, T.; Higuchi M.; Ikeda, I.; Ohshiro Y. *J. Chem. Soc., Chem. Commun.* **1993**, 194−195.

[11] This was confirmed by the visual observation of the reaction mixture through sapphire windows placed on top and bottom covers of the autoclave.

TABLE 1. Reaction of Amines 2a-c with DMC at Different Pressures of CO_2

				products (%, GC, after 2 h)			
entry[a]	RNH_2, R	P_{CO_2} (bar)	convn[b] (%)	RNHMe	$RNMe_2$	$RNHCO_2Me$	$RN(Me)CO_2Me$
1	**2a**: Bn	5	52	14	8	27	2
2		6	50	14	8	25	1
3		6	55	14	9	27	2
4		42	68	10	5	51[c]	1
5		107	49	4	<1	40	
6		150	42	2	<1	32	
7		198	36	<1		24	
8	**2b**: $Ph(CH_2)_2$	5	73	14	11	46	2
9		41	85	8	5	70	2
10		105	77	7	2	67	1
11		160	55	3		52	
12		190	44	2		42	
13	**2c**: Cy	5	58	19	11	28	
14		44	62	14	5	43	
15		100	40	6		34	
16		157	9			9	
17		200	5			5	

[a] Entries 4−17: conversions and product distribution were averaged over three values which did not differ by more than 10% from each other. [b] Conversion (%) was determined by GC. [c] Carbamate **5a** was purified by FCC (eluant, diethyl ether/petroleum ether 1:4 v/v) and isolated in a 41% yield.

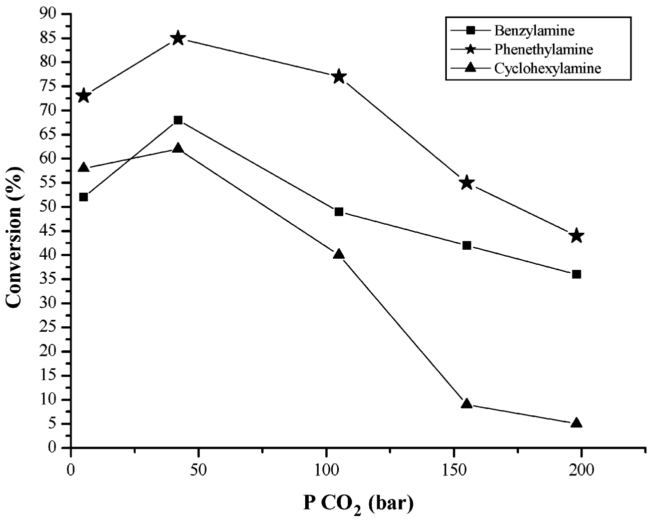

FIGURE 1. Reaction of amines **2a**−**c** with DMC/CO_2 as plots of the conversion (%, by GC) at different pressures of CO_2 and after 2 h.

In particular, opposite effects of the pressure of CO_2 can account for the observed behavior. According to Scheme 1, an increase of the CO_2 pressure favors the acid−base equilibrium between the aliphatic amine and CO_2 (reaction a), and consequently the availability of the reactant nucleophile, namely, the carbamate anion ($RNHCO_2^-$, **I**).[12] This may ultimately improve the reaction conversion (Figure 1, pressure range from 5 to 40 bar).[13]

Instead, at pressures higher than 40 bar, the decrease of the reaction rate may depend on different factors (a−c): (a) Let's consider the second step of the investigated reaction (Scheme 5). Although two mechanisms ($B_{Al}2$ in path a, or $B_{Ac}2$ in path b[14]) can operate, it should be noted that DMC-mediated $B_{Ac}2$ reactions are often reversible processes.[5] Accordingly, the release of CO_2 through a decarboxylation process can be hindered when the pressure of CO_2 is increased. (b) As the pressure is increased, CO_2 may act as a cosolvent that progressively reduces (by way of its low polarity) the solubility of ionic compounds in liquid DMC. In the particular case, a decreased concentration of the active nucleophile ($RNHCO_2^-RNH_3^+$) will result in a slower reaction. (c) Finally, as reported by McGhee et al.,[15] if aliphatic amines are made to react with an increasing pressure of CO_2, they undergo a reversible insertion of 2 equiv of CO_2, yielding a carbamate dianion (**Ia**) (Scheme 6). The occurrence of this reaction offers a further explanation for the decrease of conversion in the right side of Figure 1; compound **Ia** in fact, is a much poorer nucleophile than **I**.

As far as the relative reactivity of amines **2a**−**c** (Figure 1), the following scale holds: phenethylamine > benzylamine > cyclohexylamine, and it becomes even more evident in the region of medium-to-high pressures of CO_2. Structural similarities between benzylamine and phenethylamine imply that the nucleophilicity of these substrates parallels their basicity (pK_a of 9.34 and 9.83 for **2a** and **2b**, respectively).[16,17] Hence, the less basic **2a** is also the less reactive one. By contrast, the reactivity of cyclohexylamine (pK_a = 10.58),[16] although more basic than **2a** and **2b**, is dominated by the steric hindrance around the NH_2 group. For instance, in the case of carbamate salts such as $RNHCO_2^-$ $HCyTMG^+$, cyclohexyl and *tert*-butyl (R = *t*-Bu, Cy) substituents were reported

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[12] The direct attack of the amine to the carbonyl group of DMC ($B_{Ac}2$ mechanism) can be ruled out because it requires acidic or basic catalysis. See refs 4 and 5 and Vauthey, I.; Valot, F.; Gozzi, C.; Fache, F.; Lemaire, M. *Tetrahedron Lett.* **2000**, *41*, 6347−6350.

[13] It should also be noted that if the N-methylation of reagents would not take place (especially at the lower pressure), the difference in conversions at 5 and 40 bar would probably be even more remarkable.

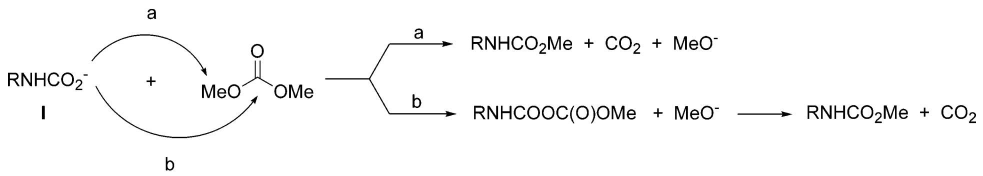
[14] Path b has been suggested by Aresta et al. (see ref 4) to account for the catalytic role of CO_2 in the carbamate synthesis.

[15] McGhee, W.; Riley, D.; Christ, K.; Pan, Y.; Parnas, B. *J. Org. Chem.* **1995**, *60*, 2820−2830.

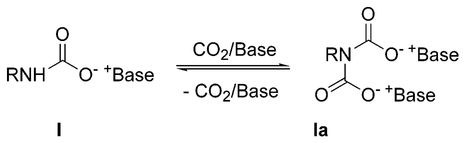
[16] Graton, J.; Laurence, C.; Berthelot, M.; Le Questel, J. Y.; Besseau, F.; Raczynska E. D. *J. Chem. Soc., Perkin. Trans. 2* **1999**, 997−1001.

[17] (a) Swain, C. G.; Scott, C. B. *J. Am. Chem. Soc.* **1953**, *75*, 141−147. (b) Pearson, G. R.; Sobel, H. Songstad, J. *J. Am. Chem. Soc.* **1968**, *90*, 319−326. (c) Bock, L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 2826−2829.

SCHEME 5



SCHEME 6



to have similar bulkiness.[15] Other kinetic investigations have shown that benzylamine is far more reactive than cyclohexylamine.[18]

(ii) The selectivity toward methyl carbamates (**5a**–**c**, $RNHCO_2Me$) is significantly improved by the increase of the CO_2 pressure because the competitive N-methylation reaction is depressed. For example, in the case of benzylamine, the total amount of *N*-methyl derivatives (**3a** + **4a**) drops from 22% to less than 5% for reactions carried out at 6 and 107 bar of CO_2, respectively (entries 2 and 5; similar conversions of 50% and 49% are compared).

To further investigate this aspect, additional experiments were run. Under the conditions of Table 1, reactions of amines **2a,b** with DMC/CO_2 were made to proceed for different times in order to get comparable conversions. Cyclohexylamine **2c** was not considered because of the very low conversion (see Table 1) observed at pressure ≥150 bar.

Figure 2A reports the results for benzylamine. As the CO_2 pressure is raised from 6 to 107 and then to 150 bar, the reaction rate progressively decreases: times of 1, 2, and 6 h (shown in parentheses) are required to reach similar conversions of 49%, 48%, and 51%, respectively. The corresponding selectivity to the desired product (**5a**) improves from 51% to 78%.[19]

Likewise, Figure 2B shows that for phenethylamine the reaction slows down when higher CO_2 pressures are used (in the range of 5, 160, and 193 bar), but the selectivity to the corresponding methyl carbamate (**5b**) increases from 63% to 93%, at conversions of 48–54%. These results are consistent with equilibrium a of Scheme 1: if the CO_2 concentration is increased, the free reactant amine (RNH_2) becomes less and less available in solution so that the corresponding N-methylation is disfavored.

Use of Cosolvents. As aforementioned, the synthesis of methyl carbamates with DMC/CO_2 takes place in a biphasic system. This raised the question of whether the reaction outcome could be changed by operating under homogeneous conditions. Experiments were run in the presence of polar and apolar cosolvents; DMSO, DMF, MeOH, DME, and CyH were chosen. Different amounts (2–4 mL) of a given solvent were added to a solution of benzylamine in DMC (1.04 M, 10 mL), and the resulting mixture was made to react at 130 °C, over 120 bar of CO_2 and for a period of 4 h. The more polar DMSO, DMF, and MeOH completely dissolved the benzylammonium benzylcarbamate ($BnNH_3^+BnNHCO_2^-$) so that reactions occurred in a single phase (Figure 3A), whereas the use of DME and CyH did not show appreciable differences as compared to reactions with DMC alone (Figure 3B). The results are reported in Table 2.

Let's first consider the reaction selectivity (S_{carb}). At comparable conversion (~60%), S_{carb} is much lower with polar cosolvents (53–56%, entries 1 and 5) than with apolar ones (84–86%, entries 7 and 9). This behavior is particularly evident using MeOH (entries 5–6) where the ratio **5a**/(**3a** + **4a**) goes from 1.2 to 2.0. The polar protic

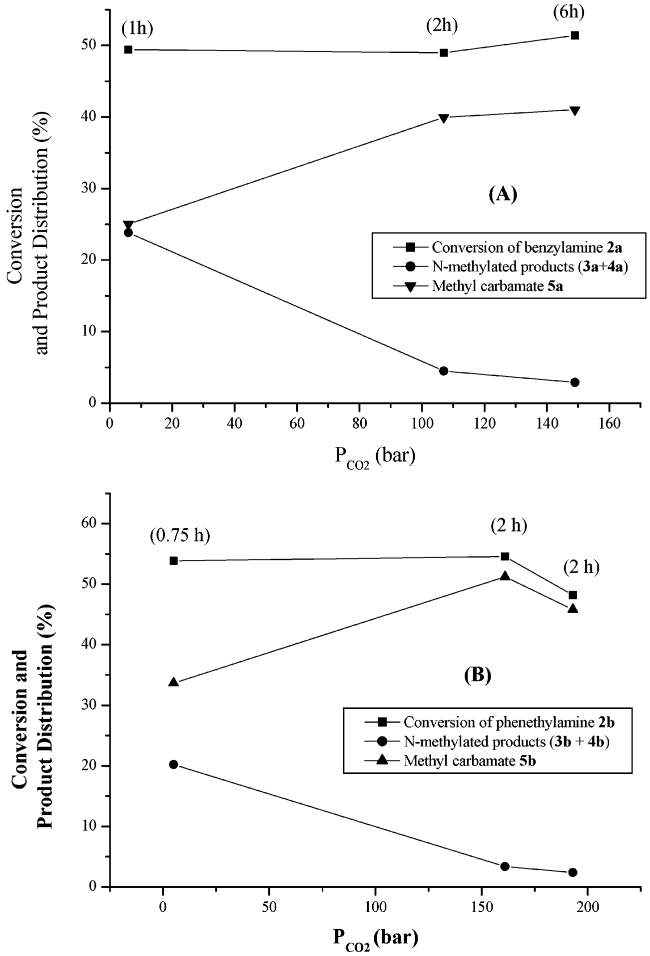


FIGURE 2. Conversion (%) and product distribution (%) as a function of the CO_2 pressure for (A) the reaction of benzylamine with DMC/CO_2 run for 1, 2, and 6 h, respectively, and (B) the reaction of phenethylamine with DMC/CO_2 run for 0.75, and 2 h, respectively. Other reaction conditions were those of Table 1.

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[18] (a) Steinmetz, A. L.; Hershberger, S. A.; Angelici, R. J. *Organometallics* **1984**, *3*, 461–468. (b) Katritzky, A. R.; Manzo, R. H. *J. Chem. Soc., Perkin Trans. 2* **1984**, 571–575. (c) Bunton, C. A.; Huang, S. K. *J. Am. Chem. Soc.* **1974**, *96*, 515–522.

[19] The selectivity for compounds **5a** is calculated as **5a**/(**3a** + **4a** + **5a** + **6a** + **7a**). For reactions of Figure 2A, the amounts of compound **7a** were of 0.5%, 4%, and 7% at 6, 107 and 150 bar, respectively; compound **6a** was detected (1%) only at 6 bar.

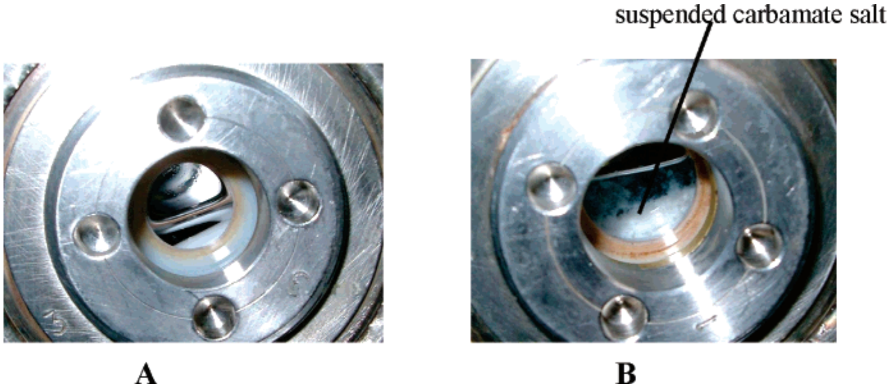


FIGURE 3. Autoclave window. The reaction of benzylamine with DMC/CO_2 (A) in the presence of DMSO, or DMF, or MeOH as cosolvents (homogeneous phase) and (B) in the presence of DMC alone or DME or CyH as cosolvents.

TABLE 2. Use of Cosolvents in Reaction of Benzylamine with DMC/CO_2^{a}

				products (%, GC)^c				
entry	ϵ^b	cosolvent (mL)	convn^c (%)	*N*-methyl derivatives (**3a** + **4a**)	**5a**	**7a**	**8a**^{d}	S_{carb} (%)^e
1	47.2	DMSO (2)	66	27	37	2		56
2		DMSO (4)	70	34	37			53
3	38.7	DMF (2)	81	5	50	3	23	62
4		DMF (4)	85	5	53	1	26	62
5	33.0	MeOH (2)	60	19	40	1		67
6		MeOH (4)	68	29	36	3		53
7	7.3	DME (2)	59	7	51	1		86
8		DME (4)	51	5	41	5		80
9	2.0	CyH (2)	62	6	52	6		84
10		CyH (4)	48	2	46			96
11	3.1^e	no cosolvent	60	6	49	2		82

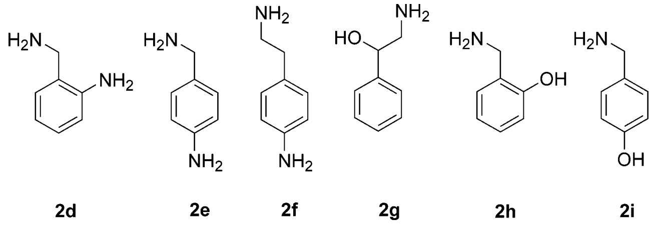
^{a} All reactions were run for 4 h under 120 bar of CO_2. ^{b} Dielectric constants at 25 °C, from Lide, D. R. *Handbook of Chemistry and Physics*, 75th ed.; CRC Press: Boca Raton, 1994; pp 6−155. ^{c} Both the conversion and the product distribution were determined from GC analyses. ^{c} Product **8a** [$PhCH_2N(Me)C(O)H$] was observed only in the reaction run with DMF. ^{d} S_{carb} (%): selectivity toward the formation of the methyl carbamate (**5a**), defined the ratio **5a** /(**3a** + **4a** + **5a** + **7a** + **8a**). ^{e} ϵ: dielectric constants of DMC at 25 °C.

medium solvates (through H-bonds) much more efficiently the anionic nucleophile ($RNHCO_2^-$) than the free amine,[20] and the N-methylation reaction becomes important. The presence of aprotic DMF enhances the nucleophilicity of anionic moieties,[21] and the corresponding **5a**/(**3a** + **4a**) ratio increases up to 11 (entry 4). Unfortunately, the side reaction of DMF with benzylamine takes over to produce *N*-benzyl,*N*-methylformamide (**8a**, $PhCH_2N(Me)C(O)H$),[22] and the overall selectivity toward the methyl carbamate **5a** drops to 62%. An apparent deviation to this trend occurs with DMSO (entries 1 and 2) whose effect, expected to be similar to that of DMF, is instead much closer to that of MeOH. Presently, there are no clear reasons for this result.[23]

As far as the reaction conversion, it slightly increases with the amount of polar cosolvents (up to 70%, entries 1 and 2, and 5 and 6),[24] whereas the converse is true with the apolar DME (entries 7 and 8) and especially, with cyclohexane (62% to 48% in entries 9 and 10). In this latter case, however, selectivity remains constant (or even slightly increases) compared to DMC alone. This suggests that the relative solubility of RNH_2 with respect to $RNHCO_2^-$ does not change and consequently the different rates of N-methylation/methoxycarbonylation (and conversion as well) are also ruled by the solvation of RNH_2 and $RNHCO_2^-$ dissolved in liquid DMC/CyH with respect to DMC. On the contrary, if the addition of apolar cosolvents would cause a drop in the concentration of ionic nucleophiles in the liquid phase, a drop in selectivity would be expected as well.[25] When the process is run in a homogeneous polar phase, the higher conversion reflects a higher reaction rate—in particular, of the competitive N-methylation of amine **2a**. To conclude, although the use of cosolvents does not ameliorate the reaction outcome, it provides insights into the solvation phenomena and the nature of the nucleophilic species involved.

Reaction Chemoselectivity. To further explore the scope and limitations of the synthesis of methyl carbamates with DMC/CO_2, the reaction of some bifunctional amines was examined. In particular, aliphatic amines bearing aromatic NH_2 groups, as well as aliphatic and aromatic OH substituents, were chosen (Scheme 7).

SCHEME 7. Bifunctional Amines 2d−i Used in Reaction with DMC/CO_2



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[20] Kornblum, N.; Selzer, R.; Haberfield, P. *J. Am. Chem. Soc.* **1963**, *85*, 1148−1154.

[21] Magnera, T. F.; Caldwell, G.; Sunner, J. Ikuta, S.; Kebarle, P. *J. Am. Chem. Soc.* **1984**, *106*, 6140−6146.

[22] (a) Iwata, M.; Kuzuhara, H. *Chem. Lett.* **1989**, 2029−2030 (b). Meyers, A. I.; Marra, Jeffrey M. *Tetrahedron Lett.* **1985**, *26*, *48*, 5863−5866.

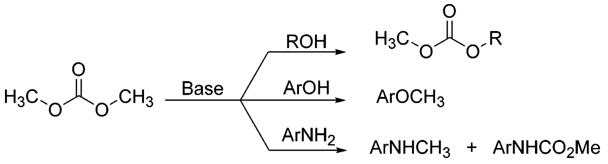
[23] DMSO is highly hygroscopic and the presence of water may account for the observed behavior.

[24] The case of DMF cannot be considered because of the concomitant formation of product **8a**.

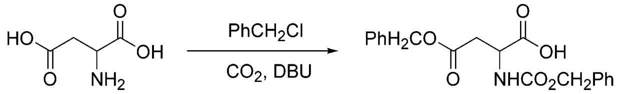
[25] It should also be noted that the addition of DME to DMC can hardly cause a decrease in the concentration of $RNHCO_2^-RNH_3^+$. In fact, the dielectric constant of DME (ϵ = 7.3) is much greater than that of CO_2 (ϵ = 1.3, fairly independent of pressure up to 300 bar. See: *Chemical Synthesis Using Supercritical Fluids*; Jessop, P. G., Leitner, W., Eds.; Wiley-VCH: 1999; Chapter 1, pp 1−36) and even greater than that of DMC (ϵ = 3.1).

Compounds **2d**−**g** were commercial products, and *o*-and *p*-hydroxybenzylamines **2h,i** were synthesized through the catalytic hydrogenation of the corresponding *o*- and *p*-hydroxybenzonitriles (see Experimental Section for details). The crucial point of this investigation was the reaction chemoselectivity. In fact, in the presence of basic catalysts, we extensively reported that DMC reacted with alcohols, phenols, and aromatic amines to yield the corresponding products of transesterification and methylation (Scheme 8).[5,7] On the other hand, the reaction of aspartic acid with CO_2 and benzyl chloride was reported to proceed with simultaneous O-alkylation and N-alcoxycarbonylation of the carboxylic and aminic groups, respectively (Scheme 9).[15] Hence, amines **2d**−**i** could, in principle, react as ambident nucleophiles with DMC yielding methylation and/or methoxycarbonylation at both the N- and O-termini.

SCHEME 8. Base: for ROH, Metal Alcoxides and Tertiary Amines; for ArOH, K_2CO_3; for $ArNH_2$, K_2CO_3 and Zeolites



SCHEME 9



Experiments were carried out under conditions similar to those of Table 1 at 130 °C. Solutions of amines **2d**−**i** in DMC (0.5 M, 8 mL) were made to react under different pressures of CO_2 in the range of 60−120 bar. Results are reported in Table 3.

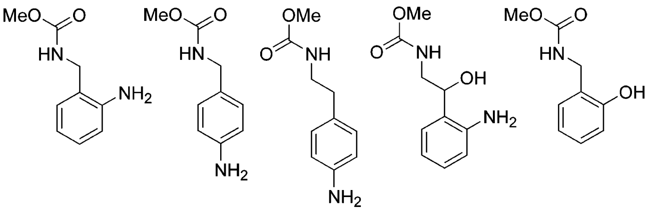
TABLE 3. Reactions of Amines 9−14 with DMC/CO_2

					$RNHCO_2Me$, **5**		
entry	substrate	*P* (bar)	*t* (h)	convn (%)		%, GC	isolated yield (%)
1	**2d**	60	4	56	**5d**	42	
2		90	4	54		45	
3			15	80		58	57
4		120	6	24		21	
5	**2e**	60	4	57	**5e**	31	
7		90	17	100		84	49
9	**2f**	90	6	66	**5f**	47	
10		90	17	100		85	45
11	**2g**	90	17	a	**5g**		65
12	**2h**	90	17	90	**5h**	64	39

[a] Neither reagent (**2g**) nor product (**5g**) were analyzable by GC or GC−MS.

The carbamate products **5d**−**h** are detailed in Scheme 10. Despite the relatively high temperature, all reactions take place with complete chemoselectivity toward the aliphatic amino groups of amines **2d**−**h**, other functionalities (aromatic NH_2 and aliphatic/aromatic OH groups) being fully preserved. As for amines **2a**−**c**, the selectivity for compounds **5d**−**h** can be increased by an increase of the CO_2 pressure, while the conversion drops (entries 1−4). Overall, better results are obtained at a pressure of 90 bar, at which the competitive N-methylation of the aliphatic NH_2 group is minimized (less than 20%). It should however be noted that only moderate isolated yields of methyl carbamates (45−49%, entries 7 and 10; compounds **5e** and **5f**, respectively) are obtained, although these products show high GC yields of 84−85%. The major reason for this difference is the difficult separation of *N*-methyl derivatives (RNHMe and $RNMe_2$, **3** and **4**) from the desired urethanes. The problem is even more severe for amine **2i** whose corresponding carbamate **5i** (its presence was suggested by the ^1H NMR analysis of the reaction mixture) cannot be isolated as a pure compound.

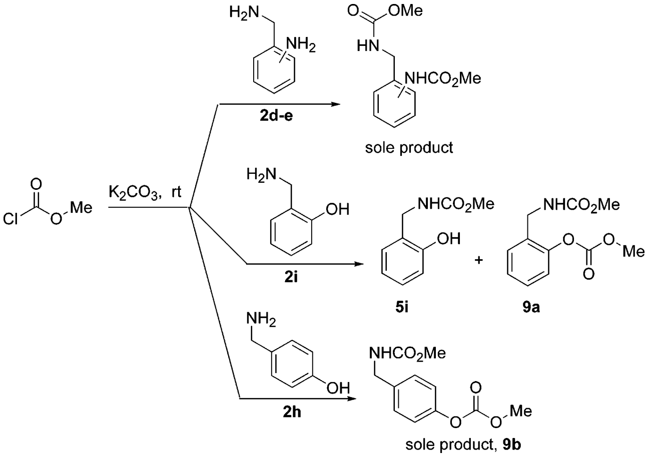
SCHEME 10. Methyl Carbamates from Amines 2d−h



5d **5e** **5f** **5g** **5h**

Finally, the present procedure was compared to a conventional method for the synthesis of methyl urethanes with $ClCO_2Me$ as the methoxycarbonylating agent.[26] Amines **2d,e** and **2h,i** were chosen as substrates. Results are reported in Scheme 11. In the case of amines **2d,e** and **2h**, a single product coming from the simultaneous methoxycarbonylation of both amino groups (compounds **2d,e**) and of both amino and hydroxyl functions (compound **2h**) was observed even at moderate conversion (50%). The reaction of amine **2i** gave a mixture of two products, the methyl carbamate **5i** and the *o*-[(*N*-methoxy carbonyl)]aminomethylphenyl methyl carbonate (**9a**) in a 3:1 ratio. In no case did the conventional procedure turn out to be a chemoselective process.[27]

SCHEME 11. Conventional Methoxycarbonylation Reactions with $ClCO_2Me$



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[26] Bortnick, N.; Luskin, L. S.; Hurwitz, M. D.; Rytina, A. W. *J. Am. Chem. Soc.* **1956**, *78*, 4358−4361.

Conclusions

The study of the reaction of primary aliphatic amines with DMC in the presence of CO_2 shows that the pressure of CO_2 affects both the reaction conversion and the selectivity. The first (conversion) plausibly reflects opposing effects on (i) the acid/base equilibrium between the reactant amine and CO_2 (Scheme 1, a), which is favored at a high CO_2 pressure, and (ii) the reactivity/solubility of $RNHCO_2^- RNH_3^+$ with/in DMC (Scheme 1, b), which on the other hand may be favored by a low pressure of CO_2. Overall, at 130 °C, conversion shows a maximum at about 40 bar. Selectivity toward methyl carbamates **5** increases continuously from 5 to 200 bar, because the competitive N-methylation of amines **2** is hindered by the increase of the CO_2 pressure.

The use of cosolvents does not significantly improve the reaction outcome, though it provides useful information on the nature and on the reactivity of the nucleophilic species involved (RNH_2 and $RNHCO_2^- RNH_3^+$).

The reaction of bifunctional amines **2d**−**i** with DMC/CO_2 proceeds with an unusual chemoselectivity: only aliphatic amino groups undergo methoxycarbonylation, while alcohols and/or aromatic NH_2 groups do not react at all. This result is not otherwise achievable with conventional procedures using $ClCO_2Me$ as a methoxycarbonylating reagent. Overall, although the reaction is quite energy intensive and yields are sometimes moderate, the method offers an ecofriendly and viable alternative for the preparation of methyl carbamates.

Experimental Section

SAFETY WARNING: Operators of high pressure equipment should take proper precautions to minimize the risks of personal injury.[28]

Reactions of Aliphatic Amines 2 with DMC in Supercritical CO_2. A stainless steel (AISI 316), jacketed autoclave of 90 mL equipped with two valves, a manometer, and two sapphire windows (fixed on the head and the bottom cover) was used as the reactor. In a typical experiment, the autoclave was charged with a solution of the amine in DMC (compounds **2a**−**c**: 1.04 M, 10 mL; compounds **2d**−**i**: 0.5 M, 8 mL), and by using an automatic syringe pump (ISCO model 260 D), CO_2 was inlet at a pressure approximately half of the desired value (in the range of 5−200 bar; see Tables 1−3). The reactor was electrically heated at 130 °C, while the reaction mixture was magnetically stirred. Then, the final pressure was reached by slowly adding further CO_2. The reaction was allowed to proceed for the reported time (Tables 1−3); after cooling, CO_2 was slowly vented by bubbling it into MeOH (5 mL). The content of the cell was washed with additional MeOH, and the combined methanolic solutions were analyzed by GC and GC−MS. The purification and characterization data of compounds **5a** and **5d** are indicated as specific examples.

Methyl *N*-Benzyl Carbamate 5a. Under the conditions of entry 4 in Table 1 (130 °C, 42 bar of CO_2), **5a** was obtained in a 51% yield by GC (conversion 68%). It was then purified by FCC on silica gel (Merck F60; eluant, diethyl ether and petroleum ether in a 1:4 v/v; $R_f = 0.3$) and isolated as a white solid (mp 59−61 °C), in a 41% yield. ^1H NMR ($CDCl_3$) δ: 3.70 (3H, s), 4.37 (2H, d, $J = 6.1$ Hz), 5.01 (1H, s broad), 7.20−7.40 (5H, m); GC−MS *m/z*: 165 (M^+, 70%), 150 ($[M - Me]^+$, 100), 133 ($[M - OMe - H]^+$, 21) 106 ($[M - COOMe]^+$, 51), 91 ($[C_7H_7]^+$, 75), 79 (42), 65 (20), 51 (19).

Methyl *N*-(2-Amino)benzyl Carbamate 5d. Under the conditions of entry 3 in Table 3 (130 °C, 90 bar of CO_2), **5d** was obtained in a 58% amount by GC (conversion 80%). It was then purified by FCC on Al_2O_3 (Macheray-Nagel; eluant, CH_2Cl_2, MeOH, aq NH_3 9:1:0.1 v/v/v; $R_f = 0.4$) and isolated as a yellow viscous oil, in a 57% yield. GC−MS (70 eV) *m/z*: 180 (M^+, 100%), 165 ($[M - Me]^+$, 17), 147 ($[M - OMe - 2H]^+$, 16) 121 ($[M - COOMe]^+$, 97), 106 ($[M - NHCOOMe]^+$, 45), 94 (29), 77 (22). ^1H NMR ($CDCl_3$, Figure 1a) δ: 3.69 (3H, s), 4.29 (2H, d, $J = 6.2$ Hz), 4.97 (1H, s broad), 6.60−7.20 (4H, m). ^{13}C NMR (DMSO-d_6, Figure 1b) δ: 157.1, 145.9, 128.5, 127.7, 122.4, 115.7, 114.6, 51.4, 40.8. IR (cm^{-1}) (KBr): 3363 (NH, stretching), 2949, 1703 (CO, stretching), 1529, 1460, 1263.

Other methyl carbamates **5** were purified by FCC; their physical and spectroscopic data are reported in Supporting Information.

Reactions with Cosolvents. Table 2. Reactions were run using the above-described procedure on the condition that initial solutions of amines in DMC were also added with a volume (2−4 mL) of a cosolvent (DMSO, DMF, MeOH, DME, and CyH).

Reactions of Amines 2a−e and 2h−i with Methyl Chloroformate. Scheme 11. A procedure of methoxycarbonylation of amines with $ClCO_2Me$ was used.[26] In a 10-mL flask, the amine (0.5 g) was dissolved in toluene (3 mL) and an aqueous solution of K_2CO_3 (1.7 M, 3 mL) was added. The resulting biphasic system was vigorously stirred and cooled to 0 °C. Then, $ClCO_2Me$ (in a 1.2 molar excess with respect to the amine) was slowly dropped to the mixture. After 30 min, diethyl ether (2 × 5 mL) was added to extract the organic phase. The combined ethereal solutions were dried over Na_2SO_4 and filtered. When necessary, products were purified by FCC or directly characterized by NMR and GC−MS. Spectroscopic data are reported in Supporting Information.

Acknowledgment. MIUR is gratefully acknowledged for financial support.

Supporting Information Available: Isolation methods and characterization data (^1H and ^{13}C NMR, GC−MS, and IR spectra) of methyl carbamates **5a**−**m** and of methyl carbonates **9a,b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) Only for the reaction of the *p*-aminophenethylamine (**2f**) with $ClCO_2Me$, the selective formation of the carbamate **5f** was reported, though a very low temperature (−78 °C) was necessary. Prugh, J. D.; Birchenough, L. A.; Egbertson, M. S. *Synth. Commun.* **1992**, *16*, 2357−60.

(28) Jessop, P. G.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 344−355.